



**UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office**

Address: Box ISSUE FEE
COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

18N2/0607

GENENTECH, INC.
GINGER R. DREGER
460 POINT SAN BRUNO BOULEVARD
SOUTH SAN FRANCISCO, CA 94080

**NOTICE OF ALLOWANCE
AND ISSUE FEE DUE**

- ☐ Note attached communication from the Examiner
☐ This notice is issued in view of applicant's communication filed _____

SERIES CODE/SERIAL NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT	DATE MAILED
09/035,427	03/22/93	026	ALLEN, M	1812 06/07/94
First Named Applicant ANDERSON, STEPHEN				

TITLE OF INVENTION
VARIANTS OF TISSUE PLASMINOGEN ACTIVATOR, COMPOSITIONS AND METHODS OF USE FOR SAME (AS AMENDED)

	ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
1	488P1C2	435-240.200	B43	UTILITY	NO	\$1170.00	09/07/94

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED.

THE ISSUE FEE MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED.

HOW TO RESPOND TO THIS NOTICE:

I. Review the SMALL ENTITY Status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

- A. If the Status is changed, pay twice the amount of the FEE DUE shown above and notify the Patent and Trademark Office of the change in status; or
B. If the Status is the same, pay the FEE DUE shown above.

If the SMALL ENTITY is shown as NO:

- A. Pay FEE DUE shown above, or
B. File verified statement of Small Entity Status before, or with, payment of 1/2 the FEE DUE shown above.

- II. Part B of this notice should be completed and returned to the Patent and Trademark Office (PTO) with your ISSUE FEE. Even if the ISSUE FEE has already been paid by a charge to deposit account, Part B should be completed and returned. If you are charging the ISSUE FEE to your deposit account, Part C of this notice should also be completed and returned.
- III. All communications regarding this application must give series code (or filing date), serial number and batch number. Please direct all communications prior to issuance to Box ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees.

PATENT AND TRADEMARK OFFICE COPY

1. CORRESPONDENCE ADDRESS

18N2/0697

GENENTECH, INC.
 GINGER R. BREGER
 460 POINT SAN BRUNO BOULEVARD
 SOUTH SAN FRANCISCO, CA 94080

SERIES CODE/SERIAL NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT	DATE MAILED
08/085,427	02/22/93	026	ALLEN, M	1012 06/07/94
First Named Applicant	STEPHEN			

TITLE OF INVENTION

VARIANTS OF TISSUE PLASMINOGEN ACTIVATOR, COMPOSITIONS AND METHODS OF USE FOR SAME (AS AMENDED)

ATTY & AGENT NO.	CLASS-SUBCLASS	BATCH NO.	APPLN TYPE	SMALL ENTITY	FEE DUE	DATE DUE
1 8881102	435-240,200	B43	UTILITY	NO	\$1170.00	09/07/94

DO NOT USE THIS SPACE

2a. The following fees are enclosed:

☐ Issue Fee ☐ Advanced Order - # of Copies _____
 (Minimum of 10)

2b. The following fees should be charged to:

DEPOSIT ACCOUNT NUMBER 07/0630

☒ Issue Fee ☒ Advanced Order - # of Copies 10 +
☐ Any Deficiencies in Enclosed Fees (Minimum of 10)

The COMMISSIONER OF PATENTS AND TRADEMARKS is requested to apply the Issue Fee to the application identified above.

(Signature of party in interest of record)

(Date)

8/23/94

NOTE: The Issue Fee will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the Patent and Trademark Office.

TRANSMIT THIS FORM WITH PART B WHEN AUTHORIZING USE OF A DEPOSIT ACCOUNT

PART B - ISSUE FEE TRANSMITTAL

MAILING INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE. Blocks 2 through 6 should be completed where appropriate. All further correspondence including the Issue Fee Receipt, the Patent, advanced orders and notification of maintenance fees will be mailed to addressee entered in Block 1 unless you direct otherwise, by: (a) specifying a new correspondence address in Block 3 below; or (b) providing the PTO with a separate "FEE ADDRESS" for maintenance fee notifications with the payment of Issue Fee or thereafter. See reverse for Certificate of Mailing.

1. CORRESPONDENCE ADDRESS

18N2/0607
 GENENTECH, INC.
 GINGER R. DREGER
 460 POINT SAN BRUNO BOULEVARD
 SOUTH SAN FRANCISCO, CA 94060

2. INVENTOR(S) ADDRESS CHANGE (Complete only if there is a change)

INVENTOR'S NAME

Street Address

City, State and ZIP Code

CO-INVENTOR'S NAME

Street Address

City, State and ZIP Code

☐ Check if additional changes are on reverse side

SERIES CODE/SERIAL NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT	DATE MAILED
09/035,427	03/22/93	026	ALLEN, M	1812 06/07/94
First Named Applicant: ANDERSON, STEPHEN				

TITLE OF INVENTION: VARIANTS OF TISSUE PLASMINOGEN ACTIVATOR, COMPOSITIONS AND METHODS OF USE FOR SAME (AS AMENDED)

ATTYS DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
188P102	435-240.200	B43	UTILITY	NO	\$1170.00	09/07/94

3. Further correspondence to be mailed to the following:

4. For printing on the patent front page, list the names of not more than 3 registered patent attorneys or agents OR alternatively, the name of a firm having as a member a registered attorney or agent. If no name is listed, no name will be printed.

1 Ginger R. Dreger

2

3

DO NOT USE THIS SPACE

5. ASSIGNMENT DATA TO BE PRINTED ON THE PATENT (print or type)

(1) NAME OF ASSIGNEE:

Genentech, Inc.

(2) ADDRESS: (City & State or Country)

South San Francisco, California

(3) STATE OF INCORPORATION, IF ASSIGNEE IS A CORPORATION

Delaware

A. ☐ This application is NOT assigned.☒ Assignment previously submitted to the Patent and Trademark Office.
☐ Assignment is being submitted under separate cover. Assignments should be directed to Box ASSIGNMENTS.

PLEASE NOTE: Unless an assignee is identified in Block 5, no assignee data will appear on the patent. Inclusion of assignee data is only appropriate when an assignment has been previously submitted to the PTO or is being submitted under separate cover. Completion of this form is NOT a substitute for filing an assignment.

6a. The following fees are enclosed:

☐ Issue Fee ☐ Advanced Order - # of Copies _____

(Minimum of 10)

6b. The following fees should be charged to:

DEPOSIT ACCOUNT NUMBER 07/0630

(Enclose Part C)

☒ Issue Fee ☒ Advanced Order - # of Copies 10

☐ Any Deficiencies in Enclosed Fees

(Minimum of 10)

The COMMISSIONER OF PATENTS AND TRADEMARKS is requested to apply the Issue Fee to the application identified above.

(Signature of party in interest of record)

(Date)

8/23/94

NOTE: The Issue Fee will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the Patent and Trademark Office.

TRANSMIT THIS FORM WITH FEE-CERTIFICATE OF MAILING ON REVERSE

Certificate of Mailing

I hereby certify that this correspondence is being deposited with
the United States Postal Service with sufficient postage as first class
mail in an envelope addressed to:

Box ISSUE FEE
Commissioner of Patents and Trademarks
Washington, D.C. 20231

on 23 August 1994
(Date)

Aida A. Miclat

(Name of person making deposit)

(Signature)

23 August 1994

(Date)

Note: If this certificate of mailing is used, it can only be used to transmit the Issue Fee. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawings, must have its own certificate of mailing.

This form is estimated to take 20 minutes to complete. Time will vary depending upon the needs of the individual applicant. Any comments on the amount of time you require to complete this form should be sent to the Office of Management and Organization, Patent and Trademark Office, Washington, D.C. 20231 and to the Office of Information and Regulatory Affairs, Office of Management and Budget, Washington, D.C. 20503.



UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/035,427	03/22/93	ANDERSON	S 488P102

18N2/0607
ALLEN, M EXAMINER

GENENTECH, INC.
GINGER R. DREGER
460 POINT SAN BRUNO BOULEVARD
SOUTH SAN FRANCISCO, CA 94080

ART UNIT PAPER NUMBER

1812

13/E
NB

06/07/94

DATE MAILED:

NOTICE OF ALLOWABILITY

PART I.

- ☒ This communication is responsive to amendment filed 3/14/94
- ☒ All the claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice Of Allowance And Issue Fee Due or other appropriate communication will be sent in due course.
- ☒ The allowed claims are 1, 11-12, 16-17, 24-28, 30-31, 58-60, 62-65, 67-73 which have been renumbered
- ☐ The drawings filed on _____ are acceptable. as 1-8, 11-16, 18, 17, 19, 20, 24, 21, 25, 26, 28
- ☐ Acknowledgment is made of the claim for priority under 35 U.S.C. 119. The certified copy has [] been received. [] not been received. [] been filed in parent application Serial No. _____, filed on _____, respectively.
- ☒ Note the attached Examiner's Amendment.
- ☒ Note the attached Examiner Interview Summary Record, PTOL-413.
- ☒ Note the attached Examiner's Statement of Reasons for Allowance.
- ☐ Note the attached NOTICE OF REFERENCES CITED, PTO-892.
- ☒ Note the attached INFORMATION DISCLOSURE CITATION, PTO-1449.

PART II.

A SHORTENED STATUTORY PERIOD FOR RESPONSE to comply with the requirements noted below is set to EXPIRE THREE MONTHS FROM THE "DATE MAILED" indicated on this form. Failure to timely comply will result in the ABANDONMENT of this application. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

- ☐ Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION, PTO-152, which discloses that the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.
- ☒ APPLICANT MUST MAKE THE DRAWING CHANGES INDICATED BELOW IN THE MANNER SET FORTH ON THE REVERSE SIDE OF THIS PAPER.
 - ☒ Drawing informalities are indicated on the NOTICE RE PATENT DRAWINGS, PTO-948, attached hereto or to Paper No. 5. CORRECTION IS REQUIRED.
 - ☐ The proposed drawing correction filed on _____ has been approved by the examiner. CORRECTION IS REQUIRED.
 - ☐ Approved drawing corrections are described by the examiner in the attached EXAMINER'S AMENDMENT. CORRECTION IS REQUIRED.
 - ☒ Formal drawings are now REQUIRED.

Any response to this letter should include in the upper right hand corner, the following information from the NOTICE OF ALLOWANCE AND ISSUE FEE DUE: ISSUE BATCH NUMBER, DATE OF THE NOTICE OF ALLOWANCE, AND SERIAL NUMBER.

Attachments:

- ☒ Examiner's Amendment
- ☒ Examiner Interview Summary Record, PTOL-413
- ☒ Reasons for Allowance
- ☐ Notice of References Cited, PTO-892
- ☒ Information Disclosure Citation, PTO-1449
- ☐ Notice of Informal Application, PTO-152
- ☐ Notice re Patent Drawings, PTO-948
- ☐ Listing of Bonded Draftsmen
- ☐ Other

5 An Examiner's Amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 C.F.R. § 1.312. To ensure consideration of such an amendment, it **MUST** be submitted no later than the payment of the Issue Fee.

Amend claim 28 as follows.

ε'10 --~~28~~⁶. (Twice amended) The variant of claim ~~16~~⁴ that is rendered resistant to enzymatic cleavage by an amino acid substitution at position 275 or [the] 277 [site] or both.--

15 In claim 31, line 24, please change "N103A296A297AA298A299 t-PA to --N103A296A297A298A299 t-PA--." This corrects a clear typographical error.

Amend claim 70 as follows.

20 --~~70~~²⁵. (Amended) A composition for treating a vascular disease or condition comprising a therapeutically effective amount of t-PA variant of claim ~~68~~²⁴ in admixture with a pharmaceutically acceptable carrier.--

[ε² Amend claim 71 as follows.]

25 --~~71~~²². (Amended) A composition for treating a vascular disease or condition comprising a therapeutically effective amount of t-PA variant of claim ~~69~~²¹ in admixture with a pharmaceutically acceptable carrier.--

30 Authorization for this Examiner's Amendment was given in a telephone interview with Dr. Ginger Dreger on 23 May 1994.

35 The following is an Examiner's Statement of Reasons for Allowance:

40 Claim 15 has been canceled. Claims 1, 11-12, 16-17, 24-28, 30-31, 58-60, 62-65, and 67-73 are under consideration by the Examiner.

45 Application 07/841,698 was filed on 2/26/92 and assigned to Genentech on the same date. Application 07/480,691 was filed on 2/15/90 and assigned to Genentech on 3/30/90. The instant application 08/035,427 is a continuation of application 07/824,740 which is a continuation of application 07/480,691. According to the provisions of MPEP 306 the instant application is thereby assigned to Genentech. Reel/frame 5277/0157 refers to the 50 07/480,691 application. This establishes that the conflicting

inventions were commonly owned at the time the invention in this '698 application was made and precludes a rejection under 35 U.S.C. § 103 based upon the commonly assigned case as a reference under 35 U.S.C. § 102(f) or (g).

5 The provisional rejection of claim 59 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 12-15 of co-pending application Serial No. 07/841,698 (now refiled as 08/168,060) has been withdrawn in
10 accordance with MPEP 804.

15 The provisional rejection of claims 72 and 73 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 12-17 of co-pending application Serial No. 07/841,698 (now refiled as 08/168,060) in view of Larsen et al. (WO 87/04722) has been withdrawn in accordance with MPEP 804.

20 It is noted that claims 1-25 of application 08/168,060 have been canceled and replaced with claims 26-38. Claims 59, 72, and 73 of the instant application are drawn to methods of treatment comprising administering particular t-PA mutants. The claims of the co-pending application are drawn to methods of treatment comprising bolus administration of particular t-PA mutants. The
25 particular t-PA mutants administered are co-extensive. The claims of the instant application encompass the invention of the co-pending application as the claims of the instant application can be literally infringed without literally infringing the claims of the co-pending application. Applicant's arguments concerning the
30 unexpected results for the co-pending application's claims are not persuasive. It is noted that the co-pending application does not compare the clearance time for bolus and continuous infusion of the mutants but only compares the clearance time for bolus and continuous infusion for wild-type t-PA. The recited mutations to
35 t-PA are known to provide improved half-life and no unexpected property has been demonstrated. In addition, the results set forth in the co-pending application are not commensurate with the claims. However, as these provisional double patenting rejections are the only rejections remaining at issue in the instant application they
40 are hereby withdrawn as set forth in MPEP 804. The instant claims may form the basis for an actual, rather than provisional, double patenting rejection in the co-pending application upon issuance of the patent.

45 Any comments considered necessary by applicant must be submitted no later than the payment of the Issue Fee and, to avoid processing delays, should preferably **accompany** the Issue Fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."
50

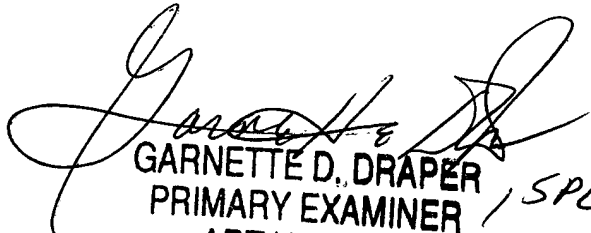
Serial No. 08/035,427
Art Unit 1812

-4-

5 Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4227.

10 Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne P. Allen whose telephone number is (703) 308-0666.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.


GARNETTE D. DRAPER
PRIMARY EXAMINER / SPE
ART UNIT 186